Hemochromatosis-associated morbidity in the United States: An analysis of the National Hospital Discharge Survey, 1979–1997

Amanda S. Brown, PhD, Marta Gwinn, MD, Mary E. Cogswell, PhD, and Muin J. Khoury, MD, PhD

Purpose: The recent discovery of the *HFE* gene and its association with hereditary hemochromatosis has renewed the attention directed to iron-overload diseases. Population screening for hereditary hemochromatosis is under debate, and population-based estimates of morbidity associated with hereditary hemochromatosis are needed. The purpose of this study is to estimate the number of hemochromatosis-associated hospitalizations in the United States using a population-based dataset. **Methods:** National Hospital Discharge Survey and census data were used to estimate hemochromatosis-associated hospitalization rates for persons 18 years of age and over. **Results:** From 1979 through 1997, the rate of hemochromatosis-associated hospitalizations was 2.3 per 100,000 persons in the United States. The rate among persons 60 years of age and over increased more than 60% during this time period. **Conclusion:** The increase in the rate of hereditary hemochromatosis-associated hospitalizations among older persons is consistent with recent trends in mortality data and may reflect the rising awareness of iron-overload disorders in the United States. ***Genetics in Medicine*, 2001:3(2):109–111.**

Key Words: *hemochromatosis, hospitalizations, iron overload, population-based, National Hospital Discharge Survey*

Hereditary hemochromatosis is a disease of primary iron overload. Complications of hereditary hemochromatosis include many common disorders e.g., cirrhosis, diabetes, cardiac disease, hyperpigmentation of the skin, and arthritis. Once thought to be rare, hereditary hemochromatosis is now understood to be one of the most common genetic disorders among the United States population. In 1996, a mutation identified in the *HFE* gene was found to be associated with the majority of hereditary hemochromatosis cases.[1] Approximately 4 to 5 per 10,000 persons of European origin are homozygous for the C282Y missense mutation;[2] an estimated 1 in 10 persons of northern European descent is a carrier. The estimated prevalence of hereditary hemochromatosis based on screening studies that use serum iron measures ranges from 2 to 5 per 1,000 persons.[3]

The identification of mutations in the *HFE* gene launched a debate about population screening for hereditary hemochromatosis using genetic testing. Although hereditary hemochromatosis meets several of the World Health Organization's criteria for screening (e.g., it can be detected before the onset of symptoms, and its complications can be prevented through the use of therapeutic phlebotomy), the justifiability of population screening for hereditary hemochromatosis is questionable because its natural history is not well understood. The phenotypic expression of hereditary hemochromatosis varies and most likely results from interactions between the genetic defect, age, sex, and environmental modifiers.[4] In addition, hereditary hemochromatosis is thought to be both underdiagnosed and under-reported. Cost-effectiveness of potential screening programs cannot accurately be assessed without additional information on the disease burden of hereditary hemochromatosis at the population level. Databases and registries can provide such information.[5] For this study, we analyzed data from the National Hospital Discharge Survey (NHDS) for 1979 through 1997 to estimate one measure of hemochromatosis-associated morbidity: the rate of hereditary hemochromatosis-associated hospitalizations in the United States.

METHODS

The NHDS is a population-based sample survey used to estimate inpatient utilization of short-stay, nonfederal hospitals in the United States.[6] The NHDS data files for 1979 through 1997 contain demographic information for over 4 million (non-newborn) hospitalizations. The NHDS data files also include up to seven International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) diagnoses per record. Each record is weighted to allow for inflation to national estimates. We selected all records that contained code 275.0 (disorders of iron metabolism, including hemochromatosis). We excluded records of persons <18 years of age to

From the Centers for Disease Control and Prevention, Atlanta, Georgia.

Amanda S. Brown, PhD, Office of Genetics and Disease Prevention, Centers for Disease Control and Prevention, Mailstop K-28, 4770 Buford Hwy NE, Atlanta, GA 30341.

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remove potential cases of pediatric hemochromatosis. We also removed records with ICD9-CM codes consistent with secondary iron overload diseases.[7] These codes included: 273.8 (hereditary atransferrinemia), 277.1 (porphyria cutanea tarda), 282.0 (hereditary spherocytosis), 282.1 (hereditary elliptocytosis), 282.3 (other hemolytic anemias due to enzyme deficiency), 282.4 (thalassemia), 282.5 (sickle cell trait), 282.6 (sickle cell anemias including 282.61 and 282.62), 282.7 (other hemoglobinopathies), 282.8 (other specified hemolytic anemias), 282.9 (hereditary hemolytic anemia), 284.0 (aplastic anemia), 284.8 (other specified aplastic anemias), 284.9 (unspecified aplastic anemia), 285.0 (sideroblastic anemia), 285.8 (congential dyserythropoietic anemia), 285.9 (unspecified anemias), and 964.0 (iron poisoning). The remaining records were considered "hereditary hemochromatosis-associated hospitalizations."

The U.S. Census Bureau population estimates for each year are included with the NHDS documentation file. We computed annual hereditary hemochromatosis-associated hospital utilization rates per 100,000 U.S. residents by using these population estimates as denominators. We calculated age-specific hereditary hemochromatosis-associated hospitalization rates for the following age groups: 18–39 years, 40–59 years, and 60 years and over.

The NHDS utilizes a stratified, multistage probability design. This complex sampling design requires special consideration for presentation of estimates and imposes limitations when standard errors are calculated for multiple-year estimates. Guidelines for reporting estimates and calculating standard errors are included in the NHDS data documentation.[6] Briefly, if the sample size is 60 or more and the relative standard error is <30%, the estimate may be reported. The relative standard error for multiple-year estimates can be determined only if the relative standard error for each single-year estimate within the year group is also computable. Thus, if a multiple-year estimate contains individual annual sample sizes <60, the relative standard error cannot be determined with certainty.

RESULTS

For the period 1979 through 1997, the NHDS contains over 3.5 million records for persons 18 years of age or older; only 675 of these records listed ICD9-CM code 275.0 among the diagnoses. Of these, 171 also listed diagnostic codes for secondary iron overload diseases, of which thalassemias and anemias were most frequent. After removing these records, 504 records remained for hereditary hemochromatosis-associated hospitalizations. Application of the analytical weights yielded an estimated 79,580 hereditary hemochromatosis-associated hospitalizations. Among these hospitalizations, code 275.0 accounted for 22% of the primary diagnoses. The primary diagnoses among the remaining 88% of records varied widely; diagnoses for diseases of the liver and heart were the most common (Table 1). Diabetes was less common as a primary diagnosis than as a codiagnosis. The mean age of patients with hereditary hemochromatosis-associated hospitalizations was age 62 years; 92% were white and 62% were male.

Table 1
Most frequent diagnoses listed on records where hemochromatosis (ICD9-CM code 275.0) was listed as a nonprimary diagnosis

Diagnosis	% primary diagnosis	% all diagnoses
Liver disease without mention of alcohol[a]	8.4	6.3
Heart disease (dysrythmias and congestive heart failure)[b]	8.0	8.1
Osteoarthritis[c]	4.1	1.6
Diabetes mellitus[d]	2.3	5.5
Unspecified essential hypertension[e]	2.7	4.2

Includes the following ICD9-CM codes: [a]571.49–572.8; [b]427.1–429.3; [c]715.15–715.95; [d]250.0–250.91; [e]401.0–401.9.

The hereditary hemochromatosis-associated hospitalization rate among U.S. residents for 1979–1997 was 2.3 per 100,000. Estimated annual rates were in the unreportable range because of small sample sizes (see Methods section). Thus, we collapsed the data into the following multiple-year groups: 1979–1982, 1983–1987, 1988–1992, and 1993–1997. We analyzed the hereditary hemochromatosis-associated hospitalization rates for each of these groups separately by age and sex. Persons 60 years of age and over had the highest rates of hereditary hemochromatosis-associated hospitalization; from 1979 through 1997, the rate in this group increased over 60%, from 5.4 per 100,000 U.S. residents during 1979–1982, to 8.0 during 1993–1997 (Table 2). Males had a consistently higher rate of hereditary hemochromatosis-associated hospitalization, particularly in the oldest age group: 8.9 per 100,000 U.S. male residents compared with 4.4 per 100,000 U.S. female residents 60 years of age and older.

When we stratified the sample by both age and sex, males 60 years of age and over were the only group with a sample size sufficient for reportable estimates. Among this group, the hereditary hemochromatosis-associated hospitalization rate increased from 8.4 per 100,000 during 1979–1982 to 11.3 per 100,000 during 1993–1997. The confidence intervals for these multiple-year estimates are not reported because of the lack of

Table 2
Rates of hemochromatosis-associated hospitalizations per 100,000 U.S. residents

Year groups	Rate (*n*)	Age in years		
		18–39	40–59	60+
79–82	2.2 (14,456)	0.7	2.5	5.4
83–87	1.7 (14,376)	0.5	1.2	4.7
88–92	2.4 (22,214)	0.5	2.2	6.7
93–97	3.0 (28,534)	0.5	2.9	8.0
79–97	2.3 (79,580)	0.5	2.2	6.3

precision of the individual annual sample sizes in the aggregate.[6]

DISCUSSION AND CONCLUSIONS

From 1979 through 1997, hereditary hemochromatosis was rarely diagnosed among hospitalized U.S. residents. Prevalence surveys suggest that 2 to 5 per 1,000 people have hereditary hemochromatosis, yet we observed a hereditary hemochromatosis-associated hospitalization rate of approximately 2 per 100,000. Although a direct comparison cannot be made, these findings suggest that either people with hereditary hemochromatosis infrequently require hospitalization or that physicians underdiagnose or under-report hemochromatosis, or both. The most frequent codiagnoses among the estimated 79,580 hereditary hemochromatosis-associated hospitalizations were diseases of the heart, liver, and joints, and diabetes. Although these diseases are among the principal end-stage complications of hereditary hemochromatosis, each was diagnosed during <10% of hospitalizations.

Using the NHDS to quantify hemochromatosis-associated morbidity in the United States has additional limitations. First, hospitalizations are only one measure of morbidity and do not represent a complete assessment of the disease burden associated with hemochromatosis. Of the people who develop symptoms as a result of hereditary hemochromatosis, only a subset will see a doctor and be hospitalized. Of those people who are hospitalized, only a subset will be diagnosed correctly with hereditary hemochromatosis as the underlying cause of their symptoms, because the clinical conditions resulting from the disease are not specific to iron overload.[8] Second, because of limited sample size, NHDS is best used to quantify diagnoses more common than hemochromatosis. For example, the sample sizes for each year were outside the range of reliability for use in calculating confidence intervals, so we could not test for significance the upward trend in the rate of hereditary hemochromatosis-associated hospitalizations.

A previous study also used data from the NHDS to examine trends in hemochromatosis-associated morbidity rates among U.S. residents.[9] This study used published reports of NCHS data and was, therefore, limited to years where diagnoses coded 275.0 were tabulated (1979 and 1983–1987). That study reported 3,000–6,000 hemochromatosis-associated hospitalizations per year. However, these estimates were not accurate because they did not exclude diagnoses associated with secondary forms of hemochromatosis.[5] Unlike the earlier report, we used the original data from NCHS to calculate hereditary hemochromatosis-associated hospitalization rates. We excluded conditions associated with secondary iron overload diseases, and found 2,000–5,000 annual hereditary hemochromatosis-associated hospitalizations for these same years.

We also extended the study period by analyzing the NHDS data for all years from 1979 through 1997. During this time, the rate of hereditary hemochromatosis-associated hospitalizations among people over 60 years of age increased 60%. This increase parallels the 60% increase in the listing of hemochromatosis on death certificates from 1979 to 1992.[10] Both findings may result from rising awareness in the United States of iron-overload diseases, particularly hereditary hemochromatosis. Because of the increased attention given hereditary hemochromatosis since 1996, when the *HFE* gene was discovered, a further increase in hereditary hemochromatosis-associated hospitalization rates may be observed as the NHDS data from 1998 and subsequent years become available.

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